ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml solution for injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Each vial contains 10 ml of solution for injection, equivalent to 1000 Units.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a vial.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adults, adolescents and children, 6 years or older with diabetes mellitus, where treatment with insulin is required.

4.2 Posology and method of administration

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues (see section 5.1).

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dose of Apidra should be individually adjusted.

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Paediatric population

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Administration

Intravenous use
Apidra can be administered intravenously. This should be carried out by health care professionals.

Apidra must not be mixed with glucose or Ringer's solution or with any other insulin.

Subcutaneous use
Apidra should be given by subcutaneous injection shortly (0-15 min) before or soon after meals or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

When used with a subcutaneous insulin infusion pump, Apidra must not be mixed with diluents or any other insulin.

Mixing with insulins
When administered as a subcutaneous injection, Apidra must not be mixed with other medicinal products except NPH human insulin.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, neutral protamine Hagedorn [NPH], lente, long-acting, etc.), source (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate doses or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin.

Adjustment of dose may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

Apidra contains metacresol, which may cause allergic reactions.

Combination of Apidra with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Apidra is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical studies were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA Organ system classes	Very common	Common	Uncommon	Rare
Metabolism and nutrition disorders	Hypoglycaemia			
Skin and subcutaneous tissue disorders		Injection site reactions Local hypersensitivity reactions		Lipodystrophy
General disorders and administration			Systemic hypersensitivity reactions	

MedDRA Organ system classes	Very common	Common	Uncommon	Rare
site conditions				

Metabolism and nutrition disorders

Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders

Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions

Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdoses with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 mg to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a healthcare professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Insulins and analogues for injection, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insulin glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. After intravenous administration, a faster onset and shorter duration of action, as well as a greater peak response were observed as compared with subcutaneous administration. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose - lowering activity as one unit of regular human insulin.

Dose proportionality

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 Units/kg, and less than proportional increase in glucose lowering effect with 0.3 Units/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 Units/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

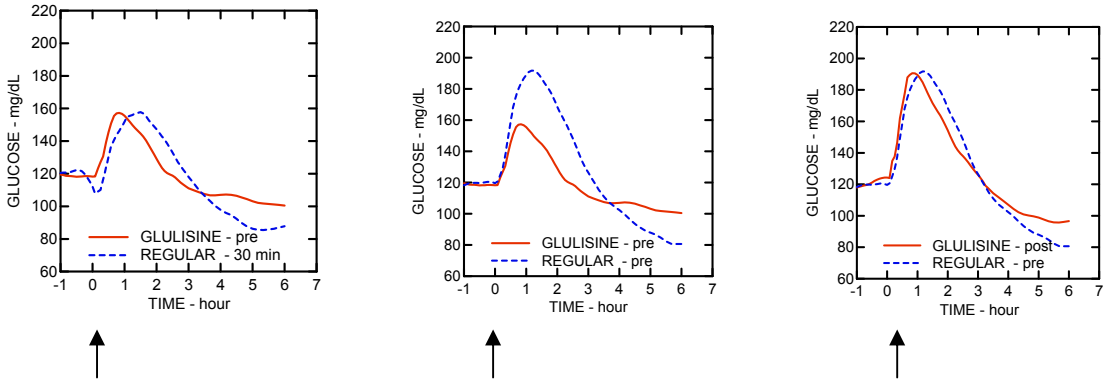


Figure 1 A Figure 1B Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20 % of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427 mg/kg for insulin glulisine, 121 minutes and 354 mg/kg for lispro, 150 minutes and 197 mg/kg for regular human insulin (see figure 2).

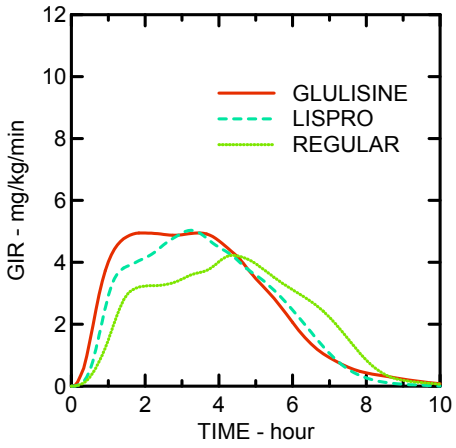


Figure 2: Glucose infusion rates (GIR) after subcutaneous injection of 0.3 Units/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid action is generally maintained across a wide range of body mass indices (BMI), while total glucose lowering effect decreases with increasing obesity.

The average total GIR AUC between 0–1 hour was 102±75 mg/kg and 158±100 mg/kg with 0.2 and 0.4 Units/kg insulin glulisine, respectively, and was 83.1±72.8 mg/kg and 112.3±70.8 mg/kg with 0.2 and 0.4 Units/kg insulin lispro respectively.

A phase I study in 18 obese patients with type 2 diabetes mellitus (BMI between 35 and 40 kg/m^2) with insulin glulisine and insulin lispro [90% CI:0.81, 0.95 (p=<0.01)] has shown that insulin glulisine effectively controls diurnal post-prandial blood glucose excursions.

Clinical studies

Type 1 diabetes mellitus-Adults
In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 1 diabetes mellitus-Paediatric
A 26-week phase III clinical study compared insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in children (4-5 years: n=9; 6-7 years: n=32 and 8-11 years: n=149) and adolescents (12-17 years: n=382) with type 1 diabetes mellitus using insulin glargine or NPH as basal insulin. Insulin glulisine was comparable to insulin lispro for glycaemic control as reflected by changes in glycated haemoglobin (GHb expressed as HbA_{1c} equivalent) from baseline to endpoint and by self-monitored blood glucose values.

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Type 2 diabetes mellitus-Adults
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58% of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displays dose-proportionality for early, maximum and total exposure in the dose range 0.075 to 0.4 Units/kg.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 Units/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µUnits/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µUnits/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure 3).

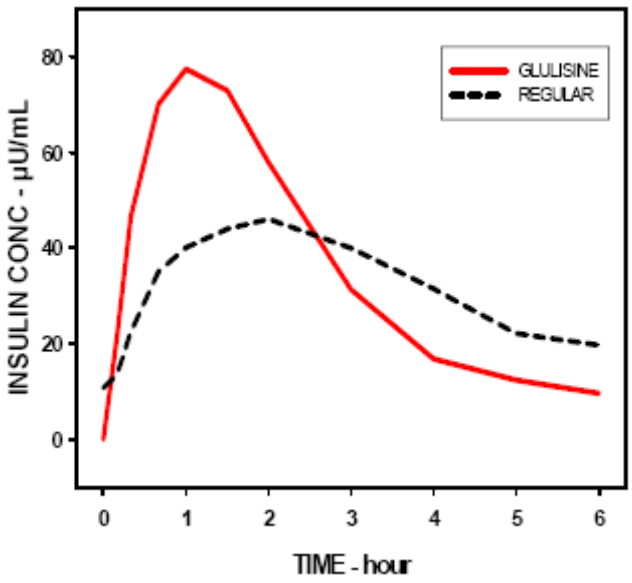


Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 Units/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 Units/kg insulin glulisine, the C_{max} was 91 µUnits/ml with the interquartile range from 78 to 104 µUnits/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similar between injection sites and of low intra-subject variability (11%CV). Intravenous bolus administration of insulin glulisine resulted in a higher systemic exposure when compared to subcutaneous injection, with a C_{max} approximately 40-fold higher.

Obesity

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid absorption and total exposure is generally maintained across a wide range of body mass indices.

The time to 10% of total INS exposure was reached earlier by approximately 5–6 min with insulin glulisine.

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.

After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801 $mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Non-clinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Subcutaneous use

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except NPH human insulin.

When used with an insulin infusion pump, Apidra must not be mixed with other medicinal products.

Intravenous use

Apidra was found to be incompatible with Glucose 5 % solution and Ringer's solution and, therefore, must not be used with these solution fluids. The use of other solutions has not been studied.

6.3 Shelf life

2 years.

Shelf life after first use of the vial

The product may be stored for a maximum of 4 weeks below 25°C away from direct heat or direct light. Keep the vial in the outer carton in order to protect from light.

It is recommended that the date of the first use from the vial be noted on the label.

Shelf life for intravenous use

Insulin glulisine for intravenous use at a concentration of 1 Unit/ml is stable between 15 C and 25 ºC for 48 hours (see section 6.6).

6.4 Special precautions for storage

Unopened vials

Store in a refrigerator (2°C - 8°C).

Do not freeze.
Do not put Apidra next to the freezer compartment or a freezer pack.
Keep the vial in the outer carton in order to protect from light.

Opened vials

For storage conditions, see section 6.3.

6.5 Nature and contents of container

10 ml solution in a vial (type I colourless glass) with a stopper (flanged aluminium overseal, elastomeric chlorobutyl rubber) and a polypropylene tear-off cap. Packs of 1, 2, 4 and 5 vials are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Subcutaneous use

Apidra vials are for use with insulin syringes with the corresponding unit scale and for use with an insulin pump system (see section 4.2).

Inspect the vial before use. It must only be used if the solution is clear, colourless, with no solid particles visible. Since Apidra is a solution, it does not require resuspension before use.

Mixing with insulins
When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

Continuous subcutaneous infusion pump
Apidra may be used for Continuous Subcutaneous Insulin Infusion (CSII) in pump systems suitable for insulin infusion with the appropriate catheters and reservoirs.

Patients using CSII should be comprehensively instructed on the use of the pump system. The infusion set and reservoir should be changed every 48 hours using aseptic technique.

Patients administering Apidra by CSII must have alternative insulin available in case of pump system failure.

Intravenous use

Apidra should be used at a concentration of 1 Unit/ml insulin glulisine in infusion systems with sodium chloride 9 mg/ml (0.9%) solution for infusion with or without 40 mmol/l potassium chloride using coextruded polyolefin/polyamide plastic infusion bags with a dedicated infusion line. Insulin glulisine for intravenous use at a concentration of 1 Unit/ml is stable at room temperature for 48 hours.

After dilution for intravenous use, the solution should be inspected visually for particulate matter prior to administration. It must only be used if the solution is clear and colourless, not when cloudy or with visible particles.

Apidra was found to be incompatible with Glucose 5% solution and Ringer's solution and, therefore, must not be used with these solution fluids. The use of other solutions has not been studied.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004
Date of latest renewal: 20 August 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml solution for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Each cartridge contains 3 ml of solution for injection, equivalent to 300 Units.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a cartridge.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adults, adolescents and children, 6 years or older with diabetes mellitus, where treatment with insulin is required.

4.2 Posology and method of administration

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues (see section 5.1).

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dose of Apidra should be individually adjusted.

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Paediatric population
There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Administration

Apidra should be given by subcutaneous injection shortly (0-15 min) before or soon after meals or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins
When administered as a subcutaneous injection, Apidra must not be mixed with other medicinal products except NPH human insulin.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate doses or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Hypoglycaemia

The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin.

Adjustment of dose may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

Pens to be used with Apidra cartridges

The Apidra cartridges should only be used with the following pens: OptiPen, ClikSTAR, Tactipen and Autopen 24 and should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

Apidra contains metacresol, which may cause allergic reactions.

Combination of Apidra with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Apidra is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breastfeeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical studies were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥ 1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA Organ system classes	**Very common**	**Common**	**Uncommon**	**Rare**
Metabolism and nutrition disorders	Hypoglycaemia			
Skin and subcutaneous tissue disorders		Injection site reactions Local hypersensitivity reactions		Lipodystrophy
General disorders and			Systemic hypersensitivity	

MedDRA Organ system classes	Very common	Common	Uncommon	Rare
administration site conditions			reactions	

Metabolism and nutrition disorders

Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders

Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions

Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdoses with insulin glulisine. However, hypoglycaemia may develop over sequential stages.

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 mg to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a healthcare professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Insulins and analogues for injection, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insulin glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose - lowering activity as one unit of regular human insulin.

Dose proportionality

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 Units/kg, and less than proportional increase in glucose lowering effect with 0.3 Units/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 Units/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

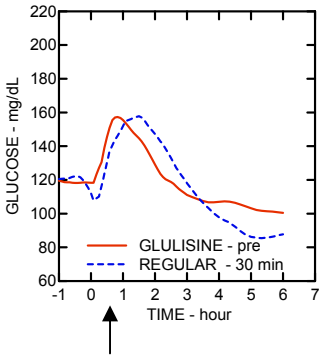


Figure 1 A

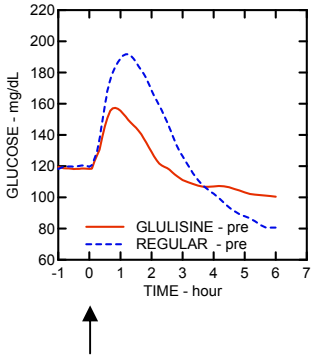


Figure 1B

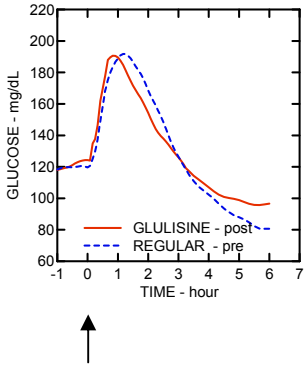


Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20 % of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427 mg/kg for insulin glulisine, 121 minutes and 354 mg/kg for lispro, 150 minutes and 197 mg/kg for regular human insulin (see figure 2).

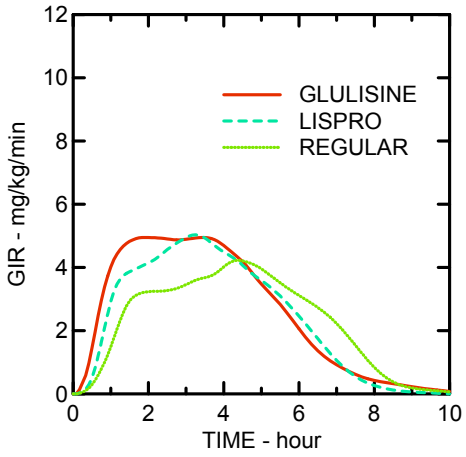


Figure 2: Glucose infusion rates (GIR) after subcutaneous injection of 0.3 Units/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid action is generally maintained across a wide range of body mass indices (BMI), while total glucose lowering effect decreases with increasing obesity.

The average total GIR AUC between 0–1 hour was 102±75 mg/kg and 158±100 mg/kg with 0.2 and 0.4 Units/kg insulin glulisine, respectively, and was 83.1±72.8 mg/kg and 112.3±70.8 mg/kg with 0.2 and 0.4 Units/kg insulin lispro respectively.

A phase I study in 18 obese patients with type 2 diabetes mellitus (BMI between 35 and 40 kg/m^2) with insulin glulisine and insulin lispro [90% CI:0.81, 0.95 (p=<0.01)]has shown that insulin glulisine effectively controls diurnal post-prandial blood glucose excursions.

Clinical studies

Type 1 diabetes mellitus-Adults

In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 1 diabetes mellitus-Paediatric
A 26-week phase III clinical study compared insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in children (4-5 years: n=9; 6-7 years: n=32 and 8-11 years: n=149) and adolescents (12-17 years: n=382) with type 1 diabetes mellitus using insulin glargine or NPH as basal insulin. Insulin glulisine was comparable to insulin lispro for glycaemic control as reflected by changes in glycated haemoglobin (GHb expressed as HbA_{1c} equivalent) from baseline to endpoint and by self-monitored blood glucose values.

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Type 2 diabetes mellitus-Adults
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58% of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displays dose-proportionality for early, maximum and total exposure in the dose range 0.075 to 0.4 Units/kg.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 Units/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µUnits/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µUnits/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure 3).

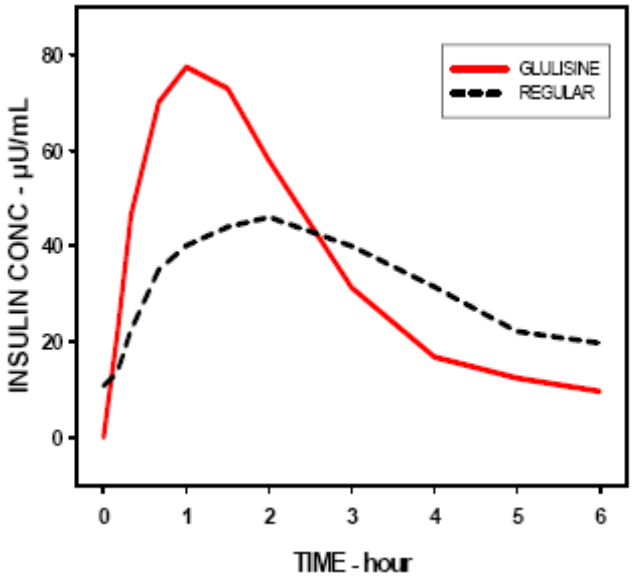


Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 Units/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 Units/kg insulin glulisine, the C_{max} was 91 µUnits/ml with the interquartile range from 78 to 104 µUnits/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similar between injection sites and of low intra-subject variability (11%CV). Intravenous bolus administration of insulin glulisine resulted in a higher systemic exposure when compared to subcutaneous injection, with a C_{max} approximately 40-fold higher.

Obesity

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid absorption and total exposure is generally maintained across a wide range of body mass indices.

The time to 10% of total INS exposure was reached earlier by approximately 5–6 min with insulin glulisine.

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.

After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801 $mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Non-clinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products except NPH human insulin.

6.3 Shelf life

2 years.

Shelf life after first use of the cartridge

The product may be stored for a maximum of 4 weeks below 25°C away from direct heat or direct light.
The pen containing a cartridge must not be stored in the refrigerator.
The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened cartridges

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Apidra next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In use cartridges

For storage conditions, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (type I colourless glass) with a plunger (elastomeric bromobutyl rubber) and a flanged cap (aluminium) with a stopper (elastomeric bromobutyl rubber). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The Apidra cartridges are to be used only in conjunction with OptiPen, ClikSTAR, Autopen 24 or Tactipen (see section 4.4). Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection. Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible. Before insertion of the cartridge into the reusable pen, the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection (see instruction for using pen). Empty cartridges must not be refilled.

If the pen malfunctions (see instructions for using the pen), the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 Units/ml) and injected. If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

To prevent any kind of contamination, the re-usable pen should be used by a single patient only.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/005-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004
Date of latest renewal: 20 August 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml solution for injection in a cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Each cartridge contains 3 ml of solution for injection, equivalent to 300 Units.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a cartridge for OptiClik.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adults, adolescents and children, 6 years or older with diabetes mellitus, where treatment with insulin is required.

4.2 Posology and method of administration

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues (see section 5.1).

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dose of Apidra should be individually adjusted.

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Paediatric population
There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Administration

Apidra should be given by subcutaneous injection shortly (0-15 min) before or soon after meals or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins
When administered as a subcutaneous injection, Apidra must not be mixed with other medicinal products except NPH human insulin.

For further details on handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate doses or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin.

Adjustment of dose may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

Apidra contains metacresol, which may cause allergic reactions.

Combination of Apidra with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Apidra is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machines). Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical studies were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥ 1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA Organ system classes	**Very common**	**Common**	**Uncommon**	**Rare**
Metabolism and nutrition disorders	Hypoglycaemia			
Skin and subcutaneous tissue disorders		Injection site reactions Local hypersensitivity reactions		Lipodystrophy
General disorders and administration site conditions			Systemic hypersensitivity reactions	

Metabolism and nutrition disorders

Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders

Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions

Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdoses with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 mg to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a healthcare professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Insulins and analogues for injection, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insulin glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose - lowering activity as one unit of regular human insulin.
Dose proportionality

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 Units/kg, and less than proportional increase in glucose lowering effect with 0.3 Units/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 Units/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

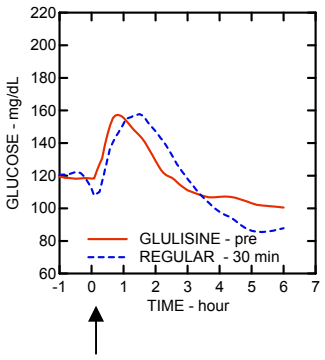


Figure 1 A

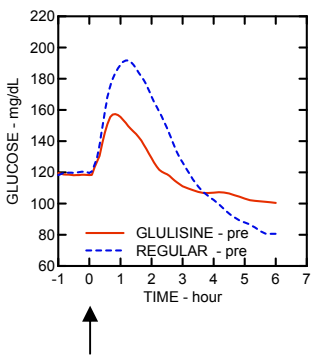


Figure 1B

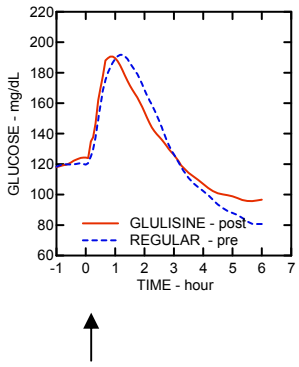


Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human

insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20 % of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427 mg/kg for insulin glulisine, 121 minutes and 354 mg/kg for lispro, 150 minutes and 197 mg/kg for regular human insulin (see figure 2).

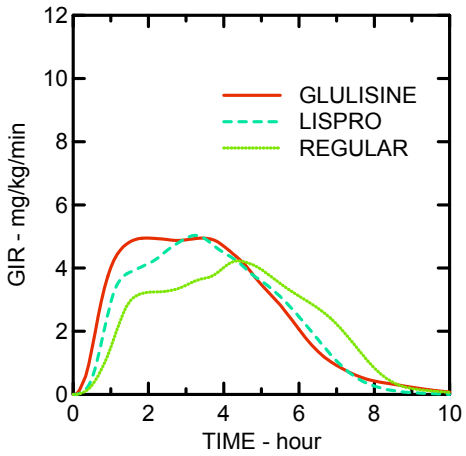


Figure 2: Glucose infusion rates (GIR) after subcutaneous injection of 0.3 Units/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid action is generally maintained across a wide range of body mass indices (BMI), while total glucose lowering effect decreases with increasing obesity.

The average total GIR AUC between 0–1 hour was 102±75 mg/kg and 158±100 mg/kg with 0.2 and 0.4 Units/kg insulin glulisine, respectively, and was 83.1±72.8 mg/kg and 112.3±70.8 mg/kg with 0.2 and 0.4 Units/kg insulin lispro respectively.

A phase I study in 18 obese patients with type 2 diabetes mellitus (BMI between 35 and 40 kg/m^2) with insulin glulisine and insulin lispro [90% CI:0.81, 0.95 (p=<0.01)]has shown that insulin glulisine effectively controls diurnal post-prandial blood glucose excursions.

Clinical studies

Type 1 diabetes mellitus-Adults
In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 1 diabetes mellitus-Paediatric
A 26-week phase III clinical study compared insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in children (4-5 years: n=9; 6-7 years: n=32 and 8-11 years: n=149) and adolescents (12-17 years: n=382) with type 1 diabetes mellitus using insulin glargine or NPH as basal insulin. Insulin glulisine was comparable to insulin lispro for glycaemic control as reflected by changes in glycated haemoglobin (GHb expressed as HbA_{1c} equivalent) from baseline to endpoint and by self-monitored blood glucose values.

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Type 2 diabetes mellitus-Adults
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58% of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

In a study with 18 male subjects with diabetes mellitus type 1, aged 21 to 50 years, insulin glulisine displays dose-proportionality for early, maximum and total exposure in the dose range 0.075 to 0.4 Units/kg.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 Units/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µUnits/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µUnits/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure 3).

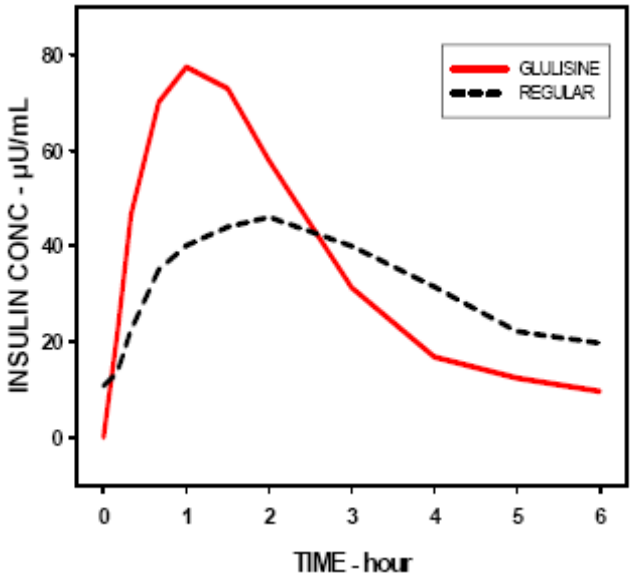


Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 Units/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 Units/kg insulin glulisine, the C_{max} was 91 µUnits/ml with the interquartile range from 78 to 104 µUnits/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similar between injection sites and of low intra-subject variability (11%CV). Intravenous bolus administration of insulin glulisine resulted in a higher systemic exposure when compared to subcutaneous injection, with a C_{max} approximately 40-fold higher.

Obesity

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid absorption and total exposure is generally maintained across a wide range of body mass indices.

The time to 10% of total INS exposure was reached earlier by approximately 5–6 min with insulin glulisine.

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.

After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801 $mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Non-clinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except NPH human insulin.

6.3 Shelf life

2 years.

Shelf life after first use of the cartridge

The product may be stored for a maximum of 4 weeks below 25°C away from direct heat or direct light. The pen containing the cartridge must not be stored in the refrigerator. The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Unopened cartridges

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Apidra next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.

In use cartridges

For storage conditions, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (type I colourless glass cartridge) with a plunger (elastomeric bromobutyl rubber) and a flanged cap (aluminium) with a stopper (elastomeric bromobutyl rubber).

The glass cartridge is irreversibly integrated in a transparent container and attached to a plastic mechanism by a threaded rod at one extremity.

Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges for OptiClik are available. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The cartridges for OptiClik are to be used in conjunction with OptiClik only, and as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection.

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used.

Before insertion of the cartridge into the reusable pen, the cartridge must be stored at room temperature for 1 to 2 hours. Inspect the cartridge before use. It must only be used if the cartridge is intact and the solution is clear, colourless, with no solid particles visible.

Air bubbles must be removed from the cartridge before injection (see instruction for using pen).
Empty cartridges must not be refilled.

If the pen malfunctions, (see instructions for using the pen) the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 Units/ml) and injected.

To prevent any kind of contamination, the re-usable pen should be used by a single patient only.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/021-028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004
Date of latest renewal: 20 August 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml solution for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Each pen contains 3 ml of solution for injection, equivalent to 300 Units.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen, OptiSet.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adults, adolescents and children, 6 years or older with diabetes mellitus, where treatment with insulin is required.

4.2 Posology and method of administration

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues (see section 5.1).

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dose of Apidra should be individually adjusted.

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Paediatric population

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Administration

Apidra should be given by subcutaneous injection shortly (0-15 min) before or soon after meals or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins
When administered as a subcutaneous injection, Apidra must not be mixed with other medicinal products except NPH human insulin.

Before using OptiSet, the Instructions for use included in the Package leaflet must be read carefully (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate doses or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin.

Adjustment of dose may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

Apidra contains metacresol, which may cause allergic reactions.

Handling of the pen
Before using OptiSet, the Instructions for use included in the Package leaflet must be read carefully. OptiSet has to be used as recommended in these Instructions for use (see section 6.6).

Combination of Apidra with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Apidra is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical studies were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA Organ system classes	**Very common**	**Common**	**Uncommon**	**Rare**
Metabolism and nutrition disorders	Hypoglycaemia			
Skin and subcutaneous tissue disorders		Injection site reactions Local hypersensitivity reactions		Lipodystrophy
General disorders and administration site conditions			Systemic hypersensitivity reactions	

Metabolism and nutrition disorders
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdoses with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 mg to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a healthcare professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Insulins and analogues for injection, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake,

especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insulin glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose - lowering activity as one unit of regular human insulin.

Dose proportionality

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 Units/kg, and less than proportional increase in glucose lowering effect with 0.3 Units/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 Units/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

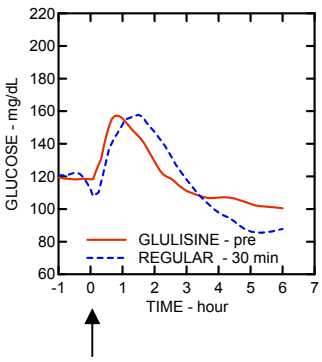


Figure 1 A

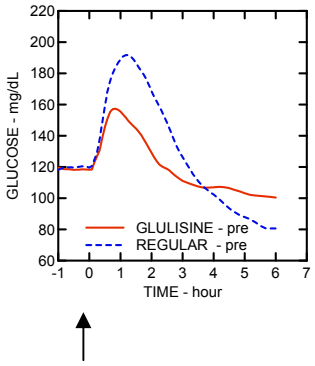


Figure 1B

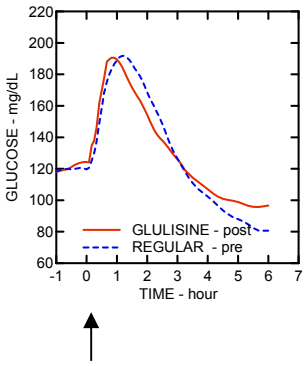


Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and

compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20 % of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427 mg/kg for insulin glulisine, 121 minutes and 354 mg/kg for lispro, 150 minutes and 197 mg/kg for regular human insulin (see figure 2).

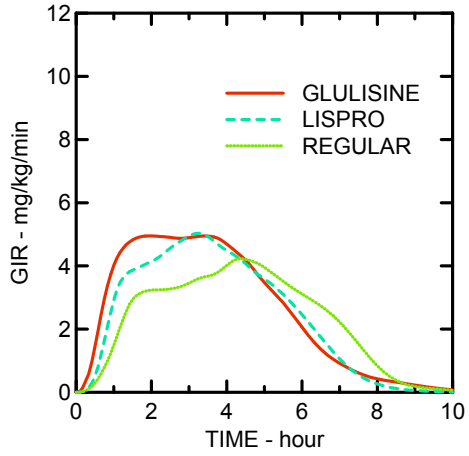


Figure 2: Glucose infusion rates (GIR) after subcutaneous injection of 0.3 Units/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid action is generally maintained across a wide range of body mass indices (BMI), while total glucose lowering effect decreases with increasing obesity.

The average total GIR AUC between 0–1 hour was 102±75 mg/kg and 158±100 mg/kg with 0.2 and 0.4 Units/kg insulin glulisine, respectively, and was 83.1±72.8 mg/kg and 112.3±70.8 mg/kg with 0.2 and 0.4 Units/kg insulin lispro respectively.

A phase I study in 18 obese patients with type 2 diabetes mellitus (BMI between 35 and 40 kg/m^2) with insulin glulisine and insulin lispro [90% CI: 0.81, 0.95 (p=<0.01)] has shown that insulin glulisine effectively controls diurnal post-prandial blood glucose excursions.

Clinical studies

Type 1 diabetes mellitus-Adults
In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 1 diabetes mellitus-Paediatric
A 26-week phase III clinical study compared insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in children (4-5 years: n=9; 6-7 years: n=32 and 8-11 years: n=149) and adolescents (12-17 years: n=382) with type 1 diabetes mellitus using insulin glargine or NPH as basal insulin. Insulin glulisine was comparable to insulin lispro for glycaemic control as reflected by changes in glycated haemoglobin (GHb expressed as HbA_{1c} equivalent) from baseline to endpoint and by self-monitored blood glucose values.

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Type 2 diabetes mellitus-Adults
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58% of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

In a study with 18 male subjects with diabetes mellitus type 1, aged 21 to 50 years, insulin glulisine displays dose-proportionality for early, maximum and total exposure in the dose range 0.075 to 0.4 Units/kg.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 Units/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µUnits/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µUnits/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure 3).

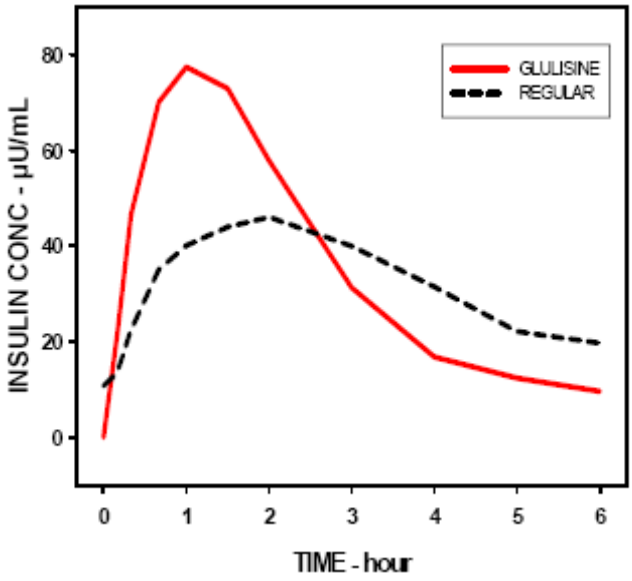


Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 Units/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 Units/kg insulin glulisine, the C_{max} was 91 µUnits/ml with the interquartile range from 78 to 104 µUnits/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similar between injection sites and of low intra-subject variability (11%CV). Intravenous bolus administration of insulin glulisine resulted in a higher systemic exposure when compared to subcutaneous injection, with a C_{max} approximately 40-fold higher.

Obesity

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid absorption and total exposure is generally maintained across a wide range of body mass indices.

The time to 10% of total INS exposure was reached earlier by approximately 5–6 min with insulin glulisine.

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.

After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801 $mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Non-clinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except NPH human insulin.

6.3 Shelf life

2 years.

Shelf life after first use of the pen:

The product may be stored for a maximum of 4 weeks below 25°C away from direct heat or direct light. Pens in use must not be stored in the refrigerator. The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Not in-use pens

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Apidra next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In use pens

For storage conditions, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (colourless glass) with a plunger (elastomeric bromobutyl rubber) and a flanged cap (aluminium) with a stopper (elastomeric bromobutyl rubber). The cartridge is sealed in a disposable pre-filled pen. Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pens are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before first use, the pen must be stored at room temperature for 1 to 2 hours.
Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since Apidra is a solution, it does not require resuspension before use.

Empty pens must never be used and must be properly discarded.

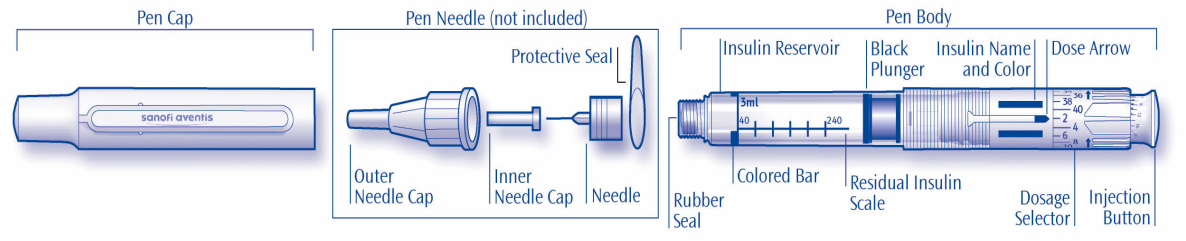
To prevent any kind of contamination, the use of the pre-filled pen should remain strictly for a single patient use.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

Handling of the pen

The patient should be advised to read the instructions for use included in the package leaflet carefully before using OptiSet.



Schematic diagram of the pen

Important information for use of OptiSet:

- A new needle must always be attached before each use. Only needles that are compatible for use with OptiSet must be used.
- A safety test must always be performed before each injection.
- If a new OptiSet is used the initial safety test must be done with the 8 units preset by the manufacturer.
- The dosage selector can only be turned in one direction.
- The dosage selector (change the dose) must never be turned after injection button has been pulled out.
- This pen is only for the patients use. It must not be shared with anyone else.
- If the injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- OptiSet must never be used if it is damaged or if the patient is not sure if it is working properly.
- The patient must always have a spare OptiSet available in case the OptiSet is lost or damaged.

Storage Instructions

Please check section 6.4 of this SPC for instructions on how to store OptiSet.

If OptiSet is in cool storage, it should be taken out 1 to 2 hours before injection to allow it to warm up. Cold insulin is more painful to inject.

The used OptiSet must be discarded as required by your local authorities.

Maintenance

OptiSet has to be protected from dust and dirt.

The outside of the OptiSet can be cleaned by wiping it with a damp cloth.

The pen must not be soaked, washed or lubricated as this may damage it.

OptiSet is designed to work accurately and safely. It should be handled with care. The patient should avoid situations where OptiSet may be damaged. If the patient is concerned that the OptiSet may be damaged, he must use a new one.

Step 1 Check the Insulin

After removing the pen cap, the label on the pen and the insulin reservoir should be checked to make sure it contains the correct insulin.

The appearance of insulin should also be checked: the insulin solution must be clear, colourless, with no solid particles visible, and must have a water-like consistency. Do not use this OptiSet if the insulin is cloudy, coloured or has particles.

Step 2 Attach the needle

The needle should be carefully attached straight onto the pen.

Step 3 Perform a safety test

Prior to each injection a safety test has to be performed.

For a new and unused OptiSet, a dose of 8 units is already preset by the manufacturer for the first safety test.

In-use OptiSet, a dose of 2 units has to be selected by turning the dosage selector forward till the dose arrow points to 2. The dosage selector will only turn in one direction.

The injection button should be pulled out completely in order to load the dose. The dosage selector must never be turned after the injection button has been pulled out.

The outer and inner needle caps should be removed. The outer cap should be kept to remove the used needle.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed all the way in.

If insulin has been expelled through the needle tip, then the pen and the needle are working properly. If no insulin appears at the needle tip, step 3 should be repeated two more times until insulin appears at the needle tip. If still no insulin comes out, change the needle, as it might be blocked and try again. If no insulin comes out after changing the needle, the OptiSet may be damaged. This OptiSet must not be used.

Step 4 Select the dose

The dose can be set in steps of 2 units, from a minimum of 2 units to a maximum of 40 units. If a dose greater than 40 units is required, it should be given as two or more injections.

The patient must always check if he has enough insulin for the dose.

The residual insulin scale on the transparent insulin reservoir shows approximately how much insulin remains in the OptiSet. This scale must not be used to set the insulin dose.

If the black plunger is at the beginning of the coloured bar, then there are approximately 40 units of insulin available.

If the black plunger is at the end of the coloured bar, then there are approximately 20 units of insulin available.

The dosage selector should be turned forward until the dose arrow points to the required dose.

Step 5 Load the dose

The injection button should be pulled out as far as it will go in order to load the pen.

The patient must always check if the selected dose is fully loaded. The injection button only goes out as far as the amount of insulin that is left in the reservoir.

The injection button allows checking the actual loaded dose. The injection button must be held out under tension during this check. The last thick line visible on the injection button shows the amount of insulin loaded. When the injection button is held out only the top part of this thick line can be seen.

Step 6 Inject the dose

The patient should be informed on the injection technique by his health care professional.
The needle should be inserted into the skin

The injection button should be pressed all the way in. A clicking sound can be heard, which will stop when the injection button has been pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle from the skin. This ensures that the full dose of insulin has been delivered.

Step 7 Remove and discard the needle

The needle should be removed after each injection and discarded. This helps prevent contamination and/or infection as well as entry of air into the insulin reservoir and leakage, of the insulin, which can cause inaccurate dosing. Needles must not be reused.

The pen cap should be replaced on the pen.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/013-020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004
Date of latest renewal: 20 August 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml solution for injection in a pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Each pen contains 3 ml of solution for injection, equivalent to 300 Units.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen, SoloStar.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adults, adolescents and children, 6 years or older with diabetes mellitus, where treatment with insulin is required.

4.2 Posology and method of administration

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues. (see section 5.1).

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dose of Apidra should be individually adjusted.

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Paediatric population

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Administration

Apidra should be given by subcutaneous injection shortly (0-15 min) before or soon after meals or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.
Mixing with insulins
When administered as a subcutaneous injection, Apidra must not be mixed with other medicinal products except NPH human insulin.

Before using SoloStar, the Instructions for use included in the Package leaflet must be read carefully (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate doses or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin. Adjustment of dose may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.
Insulin requirements may be altered during illness or emotional disturbances.

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

Apidra contains metacresol, which may cause allergic reactions.

Handling of the pen
Before using SoloStar, the Instructions for use included in the Package leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for use (see section 6.6).

Combination of Apidra with pioglitazone

Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for development of cardiac heart failure. This should be kept in mind if treatment with the combination of pioglitazone and Apidra is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machines).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical studies were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥ 1/1,000 to <1/100; rare: ≥1/10,000 to <1/1,000; very rare: <1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA Organ system classes	**Very common**	**Common**	**Uncommon**	**Rare**
Metabolism and nutrition disorders	Hypoglycaemia			
Skin and subcutaneous tissue disorders		Injection site reactions Local hypersensitivity reactions		Lipodystrophy
General disorders and administration site conditions			Systemic hypersensitivity reactions	

Metabolism and nutrition disorders
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation.

Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders and administration site conditions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdoses with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 mg to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a healthcare professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.

After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Insulins and analogues for injection, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insulin glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose - lowering activity as one unit of regular human insulin.

Dose proportionality

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 Units/kg, and less than proportional increase in glucose lowering effect with 0.3 Units/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 Units/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

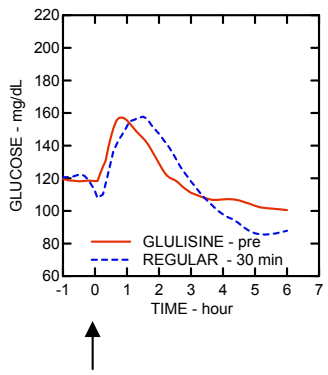


Figure 1 A

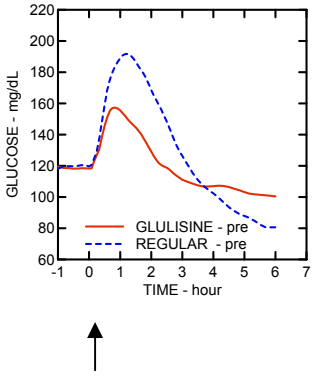


Figure 1B

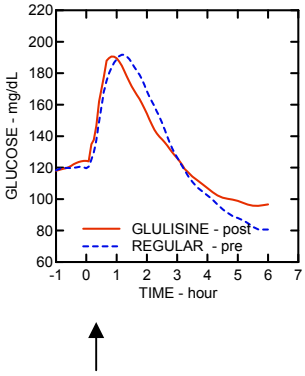


Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human

insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20 % of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427 mg/kg for insulin glulisine, 121 minutes and 354 mg/kg for lispro, 150 minutes and 197 mg/kg for regular human insulin (see figure 2).

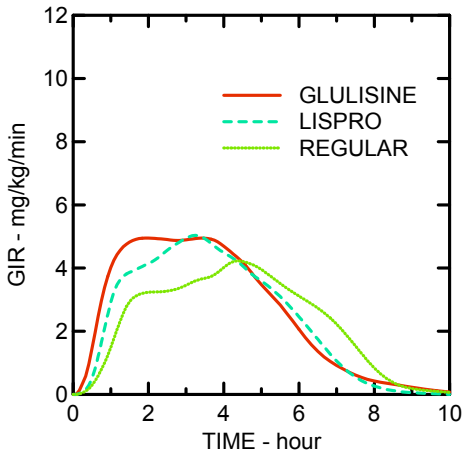


Figure 2: Glucose infusion rates (GIR) after subcutaneous injection of 0.3 Units/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid action is generally maintained across a wide range of body mass indices (BMI), while total glucose lowering effect decreases with increasing obesity.

The average total GIR AUC between 0–1 hour was 102±75 mg/kg and 158±100 mg/kg with 0.2 and 0.4 Units/kg insulin glulisine, respectively, and was 83.1±72.8 mg/kg and 112.3±70.8 mg/kg with 0.2 and 0.4 Units/kg insulin lispro respectively.

A phase I study in 18 obese patients with type 2 diabetes mellitus (BMI between 35 and 40 kg/m^2) with insulin glulisine and insulin lispro [90% CI: 0.81, 0.95 (p=<0.01)] has shown that insulin glulisine effectively controls diurnal post-prandial blood glucose excursions.

Clinical studies

Type 1 diabetes mellitus-Adults
In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 1 diabetes mellitus-Paediatric
A 26-week phase III clinical study compared insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in children (4-5 years: n=9; 6-7 years: n=32 and 8-11 years: n=149) and adolescents (12-17 years: n=382) with type 1 diabetes mellitus using insulin glargine or NPH as basal insulin. Insulin glulisine was comparable to insulin lispro for glycaemic control as reflected by changes in glycated haemoglobin (GHb expressed as HbA_{1c} equivalent) from baseline to endpoint and by self-monitored blood glucose values.

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Type 2 diabetes mellitus-Adults
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58% of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

In a study with 18 male subjects with diabetes mellitus type 1, aged 21 to 50 years, insulin glulisine displays dose-proportionality for early, maximum and total exposure in the dose range 0.075 to 0.4 Units/kg.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 Units/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µUnits/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µUnits/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure 3).

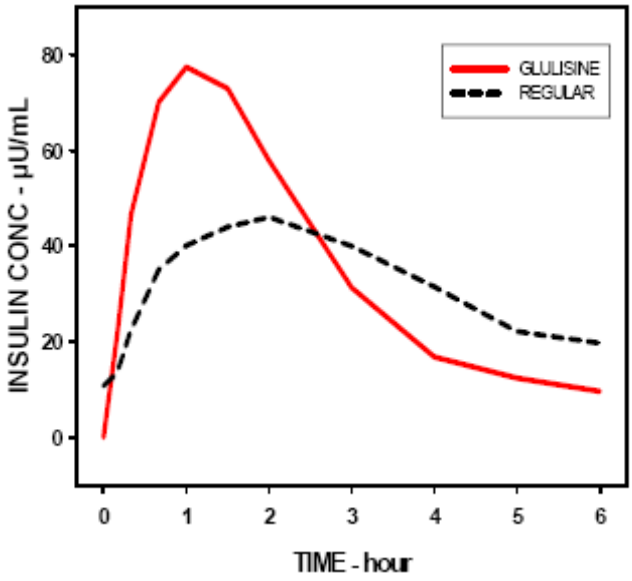


Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 Units/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 Units/kg insulin glulisine, the C_{max} was 91 µUnits/ml with the interquartile range from 78 to 104 µUnits/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similar between injection sites and of low intra-subject variability (11%CV). Intravenous bolus administration of insulin glulisine resulted in a higher systemic exposure when compared to subcutaneous injection, with a C_{max} approximately 40-fold higher.

Obesity

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid absorption and total exposure is generally maintained across a wide range of body mass indices.

The time to 10% of total INS exposure was reached earlier by approximately 5–6 min with insulin glulisine.

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.

After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801 $mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Non-clinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except NPH human insulin.

6.3 Shelf life

2 years.

Shelf life after first use of the pen
The product may be stored for a maximum of 4 weeks below 25°C away from direct heat or direct light. Pens in use must not be stored in the refrigerator. The pen cap must be put back on the pen after each injection in order to protect from light.

6.4 Special precautions for storage

Not in-use pens

Store in a refrigerator (2°C-8°C).
Do not freeze. Do not put Apidra next to the freezer compartment or a freezer pack.
Keep the pre-filled pen in the outer carton in order to protect from light.

In use pens

For storage conditions, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (colourless glass) with a plunger (elastomeric bromobutyl rubber) and a flanged cap (aluminium) with a stopper (elastomeric bromobutyl rubber). The cartridge is sealed in a disposable pre-filled pen. Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pens are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before first use, the pen must be stored at room temperature for 1 to 2 hours.

Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since Apidra is a solution, it does not require resuspension before use.

Empty pens must never be used and must be properly discarded.

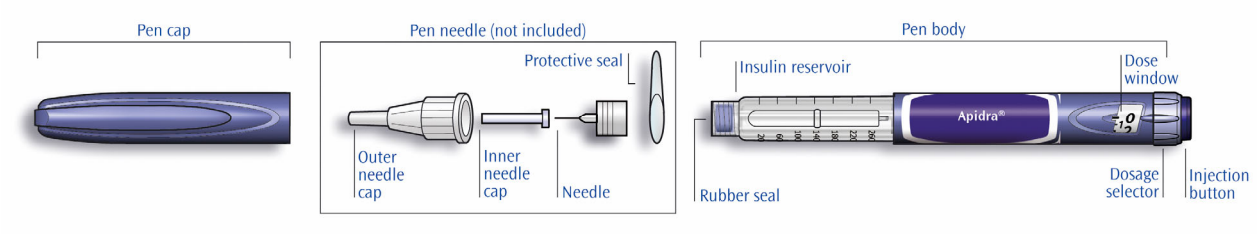
To prevent any kind of contamination, the use of the pre-filled pen should remain strictly for a single patient use.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing, as no data are available regarding the mixtures made up a significant time before injection.

Handling of the pen

The patient should be advised to read the instructions for use included in the package leaflet carefully before using SoloStar.



Schematic diagram of the pen

Important information for use of SoloStar:

- Before each use, a new needle must always be carefully attached and a safety test must be performed. Only use needles that are compatible for use with SoloStar.
- Special caution must be taken to avoid accidental needle injury and transmission of infection.
- SoloStar must never be used if it is damaged or if the patient is not sure if it is working properly.
- The patient must always have a spare SoloStar available in case the SoloStar is lost or damaged.

Storage Instructions

Please check section 6.4 for instructions on how to store SoloStar.

If SoloStar is in cool storage, it should be taken out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

The used SoloStar must be discarded as required by your local authorities.

Maintenance

SoloStar has to be protected from dust and dirt.

The outside of the SoloStar can be cleaned by wiping it with a damp cloth.

The pen must not be soaked, washed or lubricated as this may damage it.

SoloStar is designed to work accurately and safely. It should be handled with care. The patient should avoid situations where SoloStar may be damaged. If the patient is concerned that the SoloStar may be damaged, he must use a new one.

Step 1 Check the Insulin

The label on the pen should be checked to make sure it contains the correct insulin. The Apidra SoloStar is blue. It has a dark blue injection button with a raised ring on the top. After removing the pen cap, the appearance of insulin should also be checked: the insulin solution must be clear, colourless, with no solid particles visible, and must have a water-like consistency.

Step 2 Attach the needle

Only needles that are compatible for use with SoloStar should be used.
A new sterile needle will be always used for each injection. After removing the cap, the needle should be carefully attached straight onto the pen.

Step 3 Perform a safety test

Prior to each injection a safety test has to be performed.
A dose of 2 units has to be selected.
The outer and inner needle caps should be removed.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped gently with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed in completely.

If insulin has been expelled through the needle tip, then the pen and the needle are working properly.
If no insulin appears at the needle tip, step 3 should be repeated until insulin appears at the needle tip.

Step 4 Select the dose

The dose can be set in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If a dose greater than 80 units is required, it should be given as two or more injections.

The dose window must show “0” following the safety test. The dose can then be selected.

Step 5 Inject the dose

The patient should be informed on the injection technique by his health care professional.

The needle should be inserted into the skin.
The injection button should be pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle. This ensures that the full dose of insulin has been injected.

Step 6 Remove and discard the needle

The needle should always be removed after each injection and discarded. This helps prevent contamination and/or infection, entry of air into the insulin reservoir and leakage of insulin. Needles must not be reused.

Special caution must be taken when removing and disposing the needle. Recommended safety measures for removal and disposal of needles must be followed (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

The pen cap should be replaced on the pen.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/029-036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004
Date of latest renewal: 20 August 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu/

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
Germany

Name and address of the manufacturer(s) responsible for batch release

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system
The MAH must ensure that the system of pharmacovigilance, as described in version 3.0 dated 4 February 2010, presented in Module 1.8.1. of the Marketing Authorisation of Insulin glulisine, is in place and functioning before and whilst the product is on the market.

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version **1.3**, dated 8-July-2009, of the Risk Management Plan (RMP) and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:
- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

PSUR
As a consequence of the approval of the new route of administration, the PSUR cycle for Apidra should be re-started as follows:

- Six-monthly PSURs until two full years of experience with the intravenous route in the EU has been gained
- Yearly PSURs for the following two years
- Thereafter submission at 3-yearly intervals

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (10 ml vial)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in a vial
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).
Each vial contains 10 ml of solution for injection, equivalent to 1000 Units.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride (see leaflet for further information), trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide (see leaflet for further information), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a vial.
1 vial of 10ml.
2 vials of 10ml.
4 vials of 10ml.
5 vials of 10ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous or intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened vials
Store in a refrigerator. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

After first use: The product may be stored for a maximum of 4 weeks below 25°C. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/001 1 vial of 10ml
EU/1/04/285/002 2 vials of 10ml.
EU/1/04/285/003 4 vials of 10ml
EU/1/04/285/004 5 vials of 10ml.

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (10 ml vial)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra 100 Units/ml solution for injection.

Insulin glulisine.

Subcutaneous or intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (cartridge)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in a cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride (see leaflet for further information), trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide (see leaflet for further information), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a cartridge.
1 cartridge of 3ml.
3 cartridges of 3ml.
4 cartridges of 3ml.
5 cartridges of 3ml.
6 cartridges of 3ml.
8 cartridges of 3ml.
9 cartridges of 3ml.
10 cartridges of 3ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

The Apidra cartridges are to be used only in conjunction with OptiPen, ClikSTAR, Tactipen or Autopen 24.

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: the product may be stored for a maximum of 4 weeks below 25°C. Do not refrigerate.
Keep the cartridge inserted in the pen protected from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/005 1 cartridge of 3ml
EU/1/04/285/006 3 cartridges of 3ml.
EU/1/04/285/007 4 cartridges of 3ml.
EU/1/04/285/008 5 cartridges of 3ml.
EU/1/04/285/009 6 cartridges of 3ml.
EU/1/04/285/010 8 cartridges of 3ml.
EU/1/04/285/011 9 cartridges of 3ml.
EU/1/04/285/012 10 cartridges of 3ml.

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (cartridge)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra 100 Units/ml solution for injection.

Insulin glulisine

Subcutaneous use.

2. METHOD OF ADMINISTRATION

To be used with OptiPen, ClikSTAR, Tactipen, Autopen 24.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ALUMINIUM FOIL USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml solution for injection in a cartridge.
Insulin glulisine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in a cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride (see leaflet for further information), trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide (see leaflet for further information), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a cartridge for OptiClik.
1 cartridge of 3ml
3 cartridges of 3ml
4 cartridges of 3ml
5 cartridges of 3ml
6 cartridges of 3ml
8 cartridges of 3ml
9 cartridges of 3ml
10 cartridges of 3ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
To be used with OptiClik only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.
If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: The product may be stored for a maximum of 4 weeks below 25°C.Do not refrigerate.
Keep the cartridge inserted in the pen protected from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/021 1 cartridge of 3ml
EU/1/04/285/022 3 cartridges of 3ml
EU/1/04/285/023 4 cartridges of 3ml
EU/1/04/285/024 5 cartridges of 3ml
EU/1/04/285/025 6 cartridges of 3ml
EU/1/04/285/026 8 cartridges of 3ml
EU/1/04/285/027 9 cartridges of 3ml
EU/1/04/285/028 10 cartridges of 3ml

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra 100 Units/ml solution for injection.

Insulin glulisine.

Subcutaneous use.

2. METHOD OF ADMINISTRATION

To be used with OptiClik only.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED PEN for OptiSet)

1. NAME OF THE MEDICINAL PRODUCT

Apidra, 100 Units/ml solution for injection in a pre-filled pen.

Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride (see leaflet for further information), trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide (see leaflet for further information), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen. OptiSet.
1 pen of 3 ml.
3 pens of 3 ml.
4 pens of 3 ml.
5 pens of 3 ml.
6 pens of 3 ml.
8 pens of 3 ml.
9 pens of 3 ml.
10 pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

Only use needles that have been approved for use with OptiSet.

IMPORTANT INFORMATION
Always first attach a new needle before using OptiSet.
Always perform a Safety Test before using OptiSet.
Read the package leaflet fully before using OptiSet for the first time

New information for use:
- Name of the insulin is printed on the pen
- Dosage selector can only be turned in one direction

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

After first use: The product may be stored for a maximum of 4 weeks below 25°C.
Do not refrigerate.
Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/013 1 pen of 3 ml.
EU/1/04/285/014 3 pens of 3 ml.
EU/1/04/285/015 4 pens of 3 ml.
EU/1/04/285/016 5 pens of 3 ml.
EU/1/04/285/017 6 pens of 3 ml.
EU/1/04/285/018 8 pens of 3 ml.
EU/1/04/285/019 9 pens of 3 ml.
EU/1/04/285/020 10 pens of 3 ml.

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra Optiset

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (pre-filled pen OptiSet)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra, 100 Units/ml solution for injection.

Insulin glulisine.

Subcutaneous use.

2. METHOD OF ADMINISTRATION

OptiSet

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (PRE-FILLED PEN for SoloStar)

1. NAME OF THE MEDICINAL PRODUCT

Apidra, 100 Units/ml solution for injection in a pre-filled pen.

Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride (see leaflet for further information), trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide (see leaflet for further information), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen. SoloStar.
1 pen of 3 ml.
3 pens of 3 ml.
4 pens of 3 ml.
5 pens of 3 ml.
6 pens of 3 ml.
8 pens of 3 ml.
9 pens of 3 ml.
10 pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

Only use needles that are compatible for use with SoloStar.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened
Store in a refrigerator (2°C-8°C). Do not freeze. Keep the pre-filled pen in the outer carton in order to protect from light.

After its first use, the product may be stored for a maximum of 4 weeks below 25°C. Do not refrigerate. Keep the pen protected from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/029 1 pen of 3 ml.
EU/1/04/285/030 3 pens of 3 ml.
EU/1/04/285/031 4 pens of 3 ml.
EU/1/04/285/032 5 pens of 3 ml.
EU/1/04/285/033 6 pens of 3 ml.
EU/1/04/285/034 8 pens of 3 ml.
EU/1/04/285/035 9 pens of 3 ml.
EU/1/04/285/036 10 pens of 3 ml.

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra SoloStar

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (pre-filled pen SoloStar)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra, 100 Units/mlsolution for injection.

Insulin glulisine

Subcutaneous use.

2. METHOD OF ADMINISTRATION

SoloStar

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Apidra 100 Units/ml solution for injection in a vial
Insulin glulisine

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus; it may be given to adults, adolescents and children, 6 years of age and older. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

It is made by biotechnology. It has a rapid onset within 10-20 minutes and a short duration, about 4 hours.

2. BEFORE YOU USE APIDRA

Do not use Apidra
- If you are allergic (hypersensitive) to insulin glulisine or any of the other ingredients of Apidra.
- If your blood sugar is too low (hypoglycaemia), follow the guidance for hypoglycaemia (see box at the end of this leaflet).

Take special care with Apidra

Follow closely the instructions for dose, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

If you have liver or kidney problems, speak to your doctor as you may need a lower dose.

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Travel

Before travelling consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries

In the following situations, the management of your diabetes may require extra care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Using other medicines

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone", used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),

- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Using Apidra with food and drink

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia(low blood sugar levels)
- you have hyperglycaemia (high blood sugar levels).

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or operating machines).
You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Apidra

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

Apidra contains metacresol, which may cause allergic reactions.

3. HOW TO USE APIDRA

Dose

Based on your life-style and the results of your blood sugar (glucose) tests and your previous insulin usage, your doctor will determine how much Apidra you will need.

Always use Apidra exactly as your doctor has told you. You should check with your doctor if you are not sure.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate, long-acting insulin, a basal insulin or with tablets used to treat high blood sugar levels.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Method of administration

Apidra is injected under the skin (subcutaneously). It may also be given intravenously by healthcare professionals under close supervision by a doctor.

Your doctor will show you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. The effect will be slightly quicker if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

Frequency of administration

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Instructions for proper use

How to handle the vials

Apidra vials are for use with insulin syringes with the corresponding unit scale and for use with an insulin pump system.

Look at the vial before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Do not shake or mix it before use.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with Apidra, have it checked by your doctor or pharmacist.

If you have to mix two types of insulin

Apidra must not be mixed with any preparation other than NPH human insulin.

If Apidra is mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing.

How to handle an infusion pump system

Apidra must never be mixed with diluents or any other insulin when used in a pump.

Before use of Apidra in the pump system you should have received comprehensive instructions of this use. In addition, information about any action to be taken in case of illness, too high or too low blood sugar or failure of the pump system.

Use the type of pump system recommended by your doctor. Read and follow the instructions that accompany your insulin infusion pump. Follow your doctor's instructions about the basal infusion rate and the mealtime insulin boluses to be taken. To get the benefit of insulin infusion, and to detect possible malfunction of the insulin pump, you should measure your blood sugar level regularly.

The infusion set and reservoir should be changed every 48 hours using aseptic technique.

What to do in case of pump system failure?

You should always have alternative insulin available for injection under the skin in case of pump system failure.

If you use more Apidra than you should

- If you **have injected too much Apidra**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Apidra

- If you **have missed a dose of Apidra** or if you **have not injected enough insulin,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Apidra

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Apidra without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can cause side effects, although not everybody gets them.

Hypoglycaemia (low blood sugar) can be very serious. If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar, take actions to increase your blood sugar level **immediately.**

If you experience the following symptoms, contact your doctor immediately:
large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. These could be symptoms of **generalised allergy to insulin, including anaphylactic reaction, which may be life-threatening.**

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Very common reported side effects
- Hypoglycaemia

Hypoglycaemia (low blood sugar) means that there is not enough sugar in the blood. See the box at the end of this leaflet for important further information about hypoglycaemia and its treatment.

Common reported side effects
- Skin and allergic reactions

Reactions at the injection site may occur (such as reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Uncommon reported side effects
- Systemic allergic reactions

Generalised allergy to insulin. Associated symptoms may include large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

Rare reported side effect
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.

Other side effects (frequency not known) include:

- **Hyperglycaemia (high blood sugar) means that there is too much sugar in the blood.**

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. See the box at the end of this leaflet for further information.
- **Eye reactions**

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE APIDRA

Keep out of the reach and sight of children.
Do not use Apidra after the expiry date, which is stated on the carton and on the label of the vial. The expiry date refers to the last day of that month.

Unopened vials
Store in a refrigerator (2°C – 8°C).
Do not freeze.
Do not put Apidra next to the freezer compartment or a freezer pack. Keep the vial in the outer carton in order to protect from light.

Opened vials
Once in use, the vial may be stored for a maximum of 4 weeks in the outer carton below 25°C away from direct heat or direct light. Do not use the vial after this time period.
It is recommended that the date of the first use be noted on the label.
Do not use Apidra if it does not appear clear and colourless.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Apidra contains

- The active substance is insulin glulisine. Each ml of the solution contains 100 Units of insulin glulisine (equivalent to 3.49 mg). Each vial contains 10 ml of solution for injection, equivalent to 1000 Units.
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

What Apidra looks like and contents of the pack

Apidra 100 Units/ml solution for injection in a vial is a clear, colourless, aqueous solution with no particles visible.

Each vial contains 10 ml solution (1000 Units). Packs of 1, 2, 4 and 5 vials are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany.

Manufacturer:
Sanofi-Aventis Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are a person with diabetes.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?
Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Using other medicines").

Warning symptoms of hyperglycaemia
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia?
Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Using other medicines").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast : sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY:

Apidra can be administered intravenously, which should be carried out by health care professionals.
Instruction for intravenous administration
Apidra should be used at a concentration of 1 Unit/ml insulin glulisine in infusion systems with sodium chloride 9 mg/ml (0.9%) solution for infusion with or without 40 mmol/l potassium chloride using coextruded polyolefin/polyamide plastic infusion bags with a dedicated infusion line. Insulin glulisine for intravenous use at a concentration of 1 Unit/ml is stable at room temperature for 48 hours.

After dilution for intravenous use, the solution should be inspected visually for particulate matter prior to administration. Never use the solution if it has become cloudy or contains particles; use it only if it is clear and colourless.

Apidra was found to be incompatible with Glucose 5% solution and Ringer's solution and, therefore, must not be used with these solution fluids. The use of other solutions has not been studied.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Apidra 100 Units/ml solution for injection in a cartridge
Insulin glulisine

Read all of this leaflet carefully before you start using this medicine. The instructions for using the insulin pen are provided with your insulin pen. Refer to them before using your medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus; it may be given to adults, adolescents and children, 6 years of age and older. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

It is made by biotechnology. It has a rapid onset within 10-20 minutes and a short duration, about 4 hours.

2. BEFORE YOU USE APIDRA

Do not use Apidra
- If you are allergic (hypersensitive) to insulin glulisine or any of the other ingredients of Apidra.
- If your blood sugar is too low (hypoglycaemia), follow the guidance for hypoglycaemia (see box at the end of this leaflet).

Take special care with Apidra

Follow closely the instructions for dose, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

If you have liver or kidney problems, speak to your doctor as you may need a lower dose.

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Travel

Before travelling consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries

In the following situations, the management of your diabetes may require extra care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Using other medicines

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking or have taken recently any other medicines, including medicines obtained without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used for the treatment of tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),

- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Using Apidra with food and drink

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels).

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or operating machines).
You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Apidra

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

Apidra contains metacresol, which may cause allergic reactions.

3. HOW TO USE APIDRA

Dose

Based on your life-style and the results of your blood sugar (glucose) tests and your previous insulin usage, your doctor will determine how much Apidra you will need.

Always use Apidra exactly as your doctor has told you. You should check with your doctor if you are not sure.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate, long acting insulin, a basal insulin or with tablets used to treat high blood sugar levels.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Method of administration

Apidra is injected under the skin (subcutaneously).

Your doctor will show you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. The effect will be slightly quicker if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

Frequency of administration

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Instructions for proper use

How to handle the cartridges

The Apidra cartridges are to be used only in conjunction with OptiPen, ClikSTAR, Tactipen or Autopen 24 to ensure you get the correct dose. Not all of these pens may be marketed in your country.

The pen should be used as recommended in the information provided by the device manufacturer.

The manufacturer’s instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection.

Before insertion of the cartridge into the reusable pen, the cartridge must be stored at room temperature for 1 to 2 hours.

Look at the cartridge before you use it. Only use it if the solution is clear, colourless and has no visible particles in it.

Do not shake or mix it before use.

Special care before injection

Air bubbles must be removed from the cartridge before injection (see instructions for using the pen). Empty cartridges must not be refilled.

To prevent any kind of contamination, the reusable pen should be used only by you.

Problems with the insulin pen?

Refer to the manufacturer's instructions for using the pen.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

If the pen does not function well, you can draw the insulin from the cartridge into an injection syringe. Therefore, keep injection syringes and needles as well. However, use only injection syringes which are designed for an insulin concentration of 100 Units per millilitre.

If you use more Apidra than you should

- If you **have injected too much Apidra**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Apidra

- If you **have missed a dose of Apidra** or if you **have not injected enough insulin,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Apidra

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Apidra without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can cause side effects, although not everybody gets them.

Hypoglycaemia (low blood sugar) can be very serious. If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar, take actions to increase your blood sugar level **immediately.**

If you experience the following symptoms, contact your doctor immediately:
large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. These could be symptoms of **generalised allergy to insulin, including anaphylactic reaction, which may be life-threatening.**

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Very common reported side effects
- Hypoglycaemia

Hypoglycaemia (low blood sugars) means that there is not enough sugar in the blood.
See the box at the end of this leaflet for important further information about hypoglycaemia and its treatment.

Common reported side effects
- Skin and allergic reactions

Reactions at the injection site may occur (such as reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Uncommon reported side effects
- Systemic allergic reactions

Generalised allergy to insulin. Associated symptoms may include large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

Rare reported side effect
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.

Other side effects (frequency not known) include:
- **Hyperglycaemia (high blood sugar) means that there is too much sugar in the blood.**

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. See the box at the end of this leaflet for further information.
- **Eye reactions**

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE APIDRA

Keep out of the reach and sight of children.
Do not use Apidra after the expiry date, which is stated on the carton and on the label of the cartridge. The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C – 8°C).Do not freeze. Do not put Apidra next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In use cartridges
Cartridges in use (in the insulin pen) may be stored for a maximum of 4 weeks below 25°C, away from direct heat or direct light and must not be stored in a refrigerator. Do not use it after this time period.

Do not use Apidra if it does not appear clear and colourless.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Apidra contains

- The active substance is insulin glulisine. Each ml of the solution contains 100 Units of insulin glulisine (equivalent to 3.49 mg). Each cartridge contains 3 ml of solution for injection, equivalent to 300 Units.
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

What Apidra looks like and contents of the pack

Apidra 100 Units/ml solution for injection in a cartridge is a clear, colourless, aqueous solution with no particles visible.

Each cartridge contains 3 ml solution (300 Units). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany.

Manufacturer:
Sanofi-Aventis Deutschland GmbH
,
Industriepark Höchst, D-65926 Frankfurt
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are a person with diabetes.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?
Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Using other medicines").

Warning symptoms of hyperglycaemia
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia?
Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.
Why does hypoglycaemia occur?

Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Using other medicines").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,

- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Apidra 100 Units/ml solution for injection in a cartridge for OptiClik
Insulin glulisine

Read all of this leaflet carefully before you start using this medicine. The instructions for using OptiClik, the insulin pen, are provided with your OptiClik. Refer to them before using your medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus; it may be given to adults, adolescents and children, 6 years of age and older. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.
It is made by biotechnology. It has a rapid onset within 10-20 minutes and a short duration, about 4 hours.

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Do not use Apidra
- If you are allergic (hypersensitive) to insulin glulisine or any of the other ingredients of Apidra.
- If your blood sugar is too low (hypoglycaemia), follow the guidance for hypoglycaemia (see box at the end of this leaflet).

Take special care with Apidra

Follow closely the instructions for dose, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

If you have liver or kidney problems, speak to your doctor as you may need a lower dose.

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Travel

Before travelling consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries

In the following situations, the management of your diabetes may require extra care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Using other medicines

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking or have taken recently any other medicines, including medicines obtained without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),

- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Using Apidra with food and drink

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels).

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or operating machines).
You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Apidra

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

Apidra contains metacresol, which may cause allergic reactions.

3. HOW TO USE APIDRA

Dose

Based on your life-style and the results of your blood sugar (glucose) tests and your previous insulin usage, your doctor will determine how much Apidra you will need.

Always use Apidra exactly as your doctor has told you. You should check with your doctor if you are not sure.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate, long acting insulin, a basal insulin or with tablets used to treat high blood sugar levels.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Method of administration

Apidra is injected under the skin (subcutaneously).

Your doctor will show you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. The effect will be slightly quicker if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

Frequency of administration

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Instructions for proper use

How to handle the cartridges for OptiClik

Apidra in cartridge for OptiClik has been developed for use in OptiClik only**.** The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection.

Before insertion of the cartridge into the reusable pen OptiClik the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection (see instruction for using pen). Empty cartridges must not be refilled.

Look at the cartridge before you use it. Only use it if the solution is clear, colourless and has no visible particles in it.
Do not shake or mix it before use.

Problems with OptiClik?

Refer to the manufacturer's instructions for using the pen.
If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used.

To prevent any kind of contamination, the reusable pen should be used only by you.

If OptiClik does not function well, you can draw the insulin from the cartridge into a syringe for injection. Therefore, keep injection syringes and needles as well. However, use only injection syringes which are designed for an insulin concentration of 100 Units per millilitre.

If you use more Apidra than you should

- If you **have injected too much Apidra**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Apidra

- If you **have missed a dose of Apidra** or if you **have not injected enough insulin,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Apidra

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Apidra without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can cause side effects, although not everybody gets them.

Hypoglycaemia (low blood sugar) can be very serious. If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening.
If you have symptoms of low blood sugar, take actions to increase your blood sugar level **immediately.**

<u>If you experience the following symptoms, contact your doctor immediately:</u>
Large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. These could be symptoms of **generalised allergy to insulin, including anaphylactic reaction, which may be life-threatening.**

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Very common reported side effects
- Hypoglycaemia

Hypoglycaemia (low blood sugars) means that there is not enough sugar in the blood.

See the box at the end of this leaflet for important further information about hypoglycaemia and its treatment.

Common reported side effects
- Skin and allergic reactions

Reactions at the injection site may occur (such as reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Uncommon reported side effects
- Systemic allergic reactions

Generalised allergy to insulin. Associated symptoms may include large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

Rare reported side effect
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.

Other side effects (frequency not known) include:
- **Hyperglycaemia (high blood sugars) means that there is too much sugar in the blood.**

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. See the box at the end of this leaflet for further information.
- **Eye reactions**

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE APIDRA

Keep out of the reach and sight of children.
Do not use Apidra after the expiry date, which is stated on the carton and on the label of the cartridge. The expiry date refers to the last day of that month.

Unopened cartridges
Store in a refrigerator (2°C – 8°C).
Do not freeze.
Do not put Apidra next to the freezer compartment or a freezer pack. Keep the cartridge in the outer carton in order to protect from light.

In use cartridges
Cartridges in use(in the insulin pen) may be stored for a maximum of 4 weeks below 25°C, away from direct heat or direct light and must not be stored in the refrigerator. Do not use it after this time period.

Do not use Apidra if it does not appear clear and colourless.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Apidra contains

- The active substance is insulin glulisine. Each ml of the solution contains 100 Units of insulin glulisine (equivalent to 3.49 mg). Each cartridge contains 3 ml of solution for injection, equivalent to 300 Units
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

What Apidra looks like and contents of the pack

Apidra 100 Units/ml solution for injection in a cartridge is a clear, colourless, aqueous solution with no particles visible. **This cartridge is for use with OptiClik only.**

Each cartridge contains 3 ml solution (300 Units). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany.

Manufacturer:
Sanofi-Aventis Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are a person with diabetes.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may have not injected enough insulin.

Why does hyperglycaemia occur?
Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Using other medicines").

Warning symptoms of hyperglycaemia

Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia?

Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?
Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Using other medicines").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast : sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you, suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Apidra 100 Units/ml solution for injection in a pre-filled pen.
Insulin glulisine

Read all of this leaflet carefully including the Instructions for Use of Apidra, pre-filled pen, OptiSet before using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus; it may be given to adults, adolescents and children, 6 years of age and older. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

It is made by biotechnology. It has a rapid onset within 10-20 minutes and a short duration, about 4 hours.

2. BEFORE YOU USE APIDRA

Do not use Apidra
- If you are allergic (hypersensitive) to insulin glulisine or any of the other ingredients of Apidra.
- If your blood sugar is too low (hypoglycaemia), follow the guidance for hypoglycaemia (see box at the end of this leaflet).

Take special care with Apidra

Follow closely the instructions for dose, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

If you have liver or kidney problems, speak to your doctor as you may need a lower dose.

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Travel

Before travelling consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries

In the following situations, the management of your diabetes may require extra care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Using other medicines

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon(pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),

- phenothiazine derivatives(used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline]or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Using Apidra with food and drink

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels).

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or operating machines).
You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Apidra

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

Apidra contains metacresol, which may cause allergic reactions.

3. HOW TO USE APIDRA

Dose

Based on your life-style and the results of your blood sugar (glucose) tests and your previous insulin usage, your doctor will determine how much Apidra you will need.

Always use Apidra exactly as your doctor has told you. You should check with your doctor if you are not sure.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate, long acting insulin, a basal insulin or with tablets used to treat high blood sugar levels.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Method of administration

Apidra is injected under the skin (subcutaneously).

Your doctor will show you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. The effect will be slightly quicker if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

Frequency of administration

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Instructions for proper use

How to handle OptiSet

OptiSet is a pre-filled disposable pen containing insulin glulisine.

Read carefully the "OptiSet Instructions for use" included at the end of this package leaflet. You must use the pen as described in these Instructions for use.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Before use always attach a new needle, and perform a safety test. Only use needles that have been approved for use with OptiSet.

Look at the cartridge sealed in the disposable pen injector before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Do not shake or mix it before use.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with OptiSet, please refer to the Questions and Answers section of the attached OptiSet Instructions for use, or have it checked by your doctor or pharmacist.

If you use more Apidra than you should

- If you **have injected too much Apidra**, your blood sugar level may become too low (hypoglycaemia).

Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Apidra

- If you **have missed a dose of Apidra** or if you **have not injected enough insulin,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Apidra

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Apidra without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can cause side effects, although not everybody gets them.

Hypoglycaemia (low blood sugar) can be very serious. If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar, take actions to increase your blood sugar level **immediately.**

<u>If you experience the following symptoms, contact your doctor immediately:</u>
large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. They could be symptoms of **generalised allergy to insulin, including anaphylactic reaction, which may be life-threatening.**

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Very common reported side effects
- Hypoglycaemia

Hypoglycaemia (low blood sugars) means that there is not enough sugar in the blood.
See the box at the end of this leaflet for important further information about hypoglycaemia and its treatment.

Common reported side effects

- Skin and allergic reactions

Reactions at the injection site may occur (such as reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Uncommon reported side effects

- Systemic allergic reactions

Generalised allergy to insulin. Associated symptoms may include large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

Rare reported side effect

- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.

Other side effects (frequency not known) include:

- **Hyperglycaemia (high blood sugars) means there is too much sugar in the blood**

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. See the box at the end of this leaflet for further information.

- **Eye reactions**

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE APIDRA

Keep out of the reach and sight of children.

Do not use Apidra after the expiry date, which is stated on the carton and on the label of the cartridge. The expiry date refers to the last day of that month.

Not in-use pens

Store in a refrigerator (2°C - 8°C). Do not freeze. Do not put the pre-filled pen next to the freezer compartment or a freezer pack.

Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens

In use pre-filled pens may be stored for a maximum of 4 weeks below 25°C, away from direct heat or direct light and must not be stored in the refrigerator. Do not use it after this time period.

Do not use Apidra if it does not appear clear and colourless.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Apidra contains

- The active substance is insulin glulisine. Each ml of the solution contains 100 Units of insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

What Apidra looks like and contents of the pack

Apidra 100 Units/ml, solution for injection in a pre-filled pen, OptiSet. It is a clear, colourless, aqueous solution with no particles visible.
Each pen contains 3 ml solution, equivalent to 300 Units. Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pre-filled pens are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
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Manufacturer:
Sanofi-Aventis Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are a person with diabetes.

HYPERGLYCAEMIA (too high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?
Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Using other medicines").

Warning symptoms of hyperglycaemia
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia?
Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?
Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Using other medicines").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast : sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

OPTISET INSTRUCTIONS FOR USE

OptiSet is a pre-filled pen for the injection of insulin. Doses from 2 to 40 units can be set in steps of 2 units. Each pen contains multiple doses.

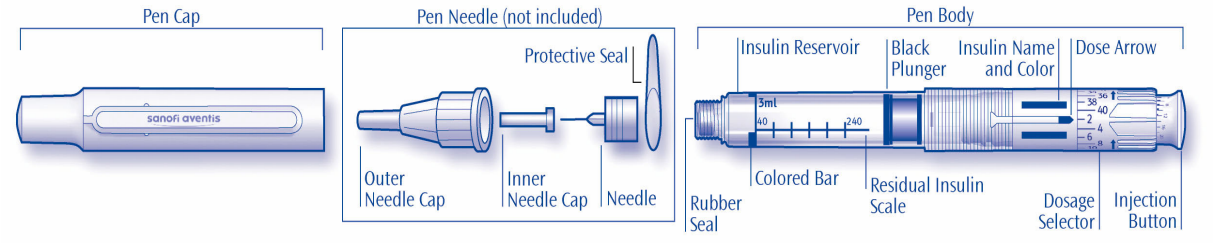
Talk with your healthcare professional about proper injection technique before using OptiSet.

Read these instructions carefully before using your OptiSet. If you are not able to follow all the instructions completely on your own, use OptiSet only if you have help from a person who is able to follow the instructions. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

Follow these instructions completely each time you use OptiSet to ensure that you get an accurate dose. If you do not follow these instructions completely, you may get too much or too little insulin, which may affect your blood glucose.

If you have any questions about OptiSet or about diabetes, ask your healthcare professional or call the local sanofi-aventis number on the front of this leaflet.

Keep this leaflet for future reference each time you use OptiSet.



Schematic diagram of the pen

New information for use:

- Name of the insulin is printed on the pen
- Dosage selector can only be turned in one direction

Important information for use of OptiSet:

- Always attach a new needle before each use. Only use needles that have been approved for use with OptiSet.
- Always perform the safety test before each injection (see Step 3).
- If you are using a new OptiSet the initial safety test must be done with the 8 units preset by the manufacturer.
- The dosage selector can only be turned in one direction.
- Never turn the dosage selector (i.e. never change the dose) after injection button has been pulled out.
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use OptiSet if it is damaged or if you are not sure that it is working properly.
- Always have a spare OptiSet in case your OptiSet is lost or damaged.

Step 1. Check the insulin

A. Take off the pen cap.

B. Check the label on your OptiSet and insulin reservoir to make sure you have the correct insulin.

C. Check the appearance of your insulin. Apidra is a clear insulin. Do not use this OptiSet if the insulin is cloudy, coloured or has particles.

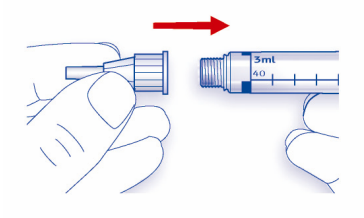
Step 2. Attach the needle

Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

Before use of needle, carefully read the "Instructions for use" accompanying the needles.
Please note: The needles shown are for illustrative purposes only.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or damage the needle.

Step 3. Perform a safety test

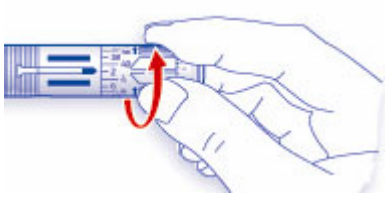
Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- making sure that pen and needle work properly
- removing air bubbles

If you are using a new OptiSet the initial safety test must be done with the 8 units preset by the manufacturer, otherwise the pen will not function properly.

A. Make sure the injection button is pressed in.

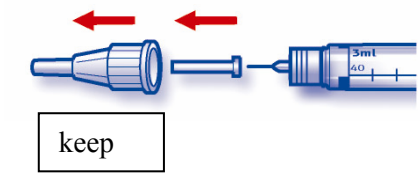
B. Select the dose for the Safety Test.

- New and unused OptiSet: a dose of 8 units is already preset by the manufacturer for the first safety test.
- In-use OptiSet: select a dose of 2 units by turning the dosage selector forward till the dose arrow points to 2. The dosage selector will only turn in one direction.



C. Pull out the injection button completely in order to load the dose. Never turn the dosage selector after injection button has been pulled out.

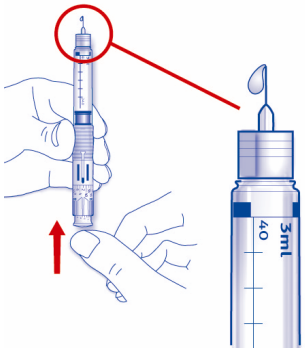
D. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



E. Hold the pen with the needle pointing upwards.

F. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

G. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

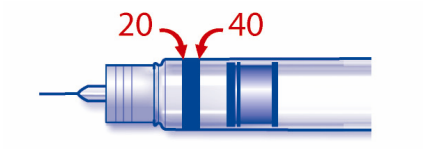
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your OptiSet may be damaged. Do not use this OptiSet.

Step 4. Select the dose

You can set the dose in steps of 2 units, from a minimum of 2 units to a maximum of 40 units. If you need a dose greater than 40 units, you should give it as two or more injections.

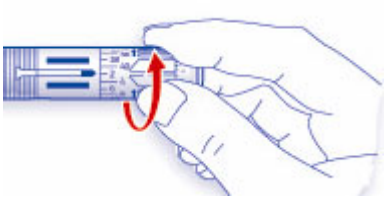
A. Check if you have enough insulin for your dose.

- The residual insulin scale on the transparent insulin reservoir shows approximately how much insulin remains in the OptiSet. This scale must not be used to set the insulin dose.
- If the black plunger is at the beginning of the coloured bar, then there are approximately 40 units of insulin available.
- If the black plunger is at the end of the coloured bar, then there are approximately 20 units of insulin available.



B. Select your required dose by turning the dose selector forward.
If you turned past your dose,

- and you have not yet pulled the injection button, you can keep turning forward till you reach your dose again,
- and you have already pulled the injection button out, you must discard the dose that has been loaded **before** you turn the dosage selector again.

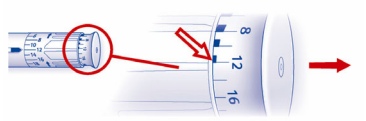


Step 5. Load the dose

A. Pull out the injection button completely in order to load the dose.

B. Check if the selected dose is fully loaded. Note that the injection button only goes out as far as the amount of insulin that is left in the reservoir.

- The injection button must be held out under tension during this check.
- The last thick line visible on the injection button shows the amount of insulin loaded. When the injection button is held out only the top part of this thick line can be seen.
- In this example, 12 units are loaded.
    - if you have selected 12 units you can inject your dose.
    - if you have selected more than 12 units then only 12 units of your total insulin dose can be injected with this pen.



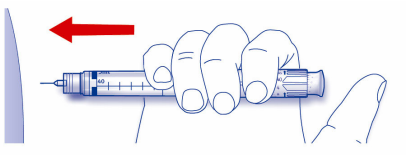
In this case what should you do:

- either you can inject what is remaining in the pen and complete your dose with a new OptiSet.
- or use a new OptiSet for your full dose.

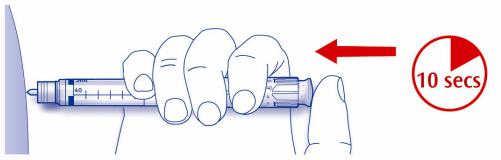
Step 6. Inject the dose

A. Use the injection method as instructed by your health care professional.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. A clicking sound can be heard, which will stop when the injection button has been pressed in completely.



D. Keep the injection button pressed in and slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin have been used.

Step 7. Remove and discard the needle

Always remove the needle after each injection and store OptiSet without a needle attached. This helps prevent:

- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

B. Dispose of the needle safely, as instructed by your healthcare professional.

C. Put the pen cap back on, then store the pen until your next injection.

Storage instructions

Please check Section 5 - How to store Apidra- of the reverse (insulin) side of this leaflet for OptiSet storage instructions.

If your OptiSet is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up to room temperature. Cold insulin is more painful to inject.

Discard your used OptiSet as required by your local regulations.

Maintenance

Protect your Optiset from dust and dirt.

You can clean the outside of your OptiSet by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your OptiSet is designed to work accurately and safely. It should be handled with care. Avoid situations where OptiSet might be damaged. If you are concerned that your OptiSet may be damaged, discard it and use a new one.

Questions and Answers

Wrong dose selected.	• Follow the instructions in Step 4 to select the correct dose.
Dose has been selected and the injection button has been pulled out and pressed in again without a needle attached.	1. Attach a new needle. 2. Press the injection button completely in and discard the insulin. 3. Perform the safety test. If the safety test is successful OptiSet is ready for use. If test is not successful, the pen might be damaged. Use a new OptiSet. If in any doubt whether the pen is working correctly use a new OptiSet.
The dosage selector does not turn.	• You are turning in the wrong direction. The dosage selector can only be turned forward. • You are turning forward while the injection button is pulled out. Press the injection button in completely to discard the dose and select again.
The amount indicated on the injection button is higher than the dose selected.	• Difference is 2 units. Discard insulin, then set your dose and check again. If the same error occurs again, OptiSet may be damaged, use a new OptiSet. • Difference is more than 2 units OptiSet is damaged, use a new OptiSet.
The amount indicated on the injection button is lower than the dose required	There is not enough insulin in the reservoir. You can do one of the following: • inject the amount indicated on the injection button from this OptiSet and then inject the remaining dose using a new OptiSet, or • inject the entire dose using a new OptiSet.
The injection button cannot be pressed in.	1. Make sure you pulled out the injection button completely. 2. Attach a new needle. 3. Press the injection button completely in to discard the insulin. Perform the safety test.
You don't hear clicking while injecting.	OptiSet is damaged, use a new OptiSet.

Insulin is leaking from the pen.	Needle may have been attached imprecisely (e.g. at a slant). Remove needle and replace with a new needle attaching it on straight (see Step 2). Perform the safety test (see Step 3).
Air bubbles are present in the reservoir.	Small amounts of air may be present in the needle and insulin reservoir during normal use. You must remove this air by performing the safety test (see Step 3). The tiny air bubbles in the insulin reservoir that do not move with tapping will not interfere with the injection and dosage.
OptiSet is damaged or is not working properly.	Do not force it. Do not try to repair or use tools on it. Use a new OptiSet.
OptiSet has been dropped or subjected to impact.	If in any doubt whether the pen is working correctly use a new OptiSet.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Apidra 100 Units/ml solution for injection in a pre-filled pen.
Insulin glulisine

Read carefully all of this leaflet including the Instructions for Use of Apidra, pre-filled pen, SoloStar before using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus; it may be given to adults, adolescents and children, 6 years of age and older. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

It is made by biotechnology. It has a rapid onset within 10-20 minutes and a short duration, about 4 hours.

2. BEFORE YOU USE APIDRA

Do not use Apidra
- If you are allergic (hypersensitive) to insulin glulisine or any of the other ingredients of Apidra.
- If your blood sugar is too low (hypoglycaemia), follow the guidance for hypoglycaemia (see box at the end of this leaflet).

Take special care with Apidra

Follow closely the instructions for dose, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

If you have liver or kidney problems, speak to your doctor as you may need a lower dose.

There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Travel

Before travelling consult your doctor. You may need to talk about
- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries

In the following situations, the management of your diabetes may require extra care:
- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Using other medicines

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:
- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:
- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics(used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),

- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),
- sympathomimetic medicines (such as epinephrine [adrenaline] or salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine, and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Using Apidra with food and drink

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels).

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or operating machines).
You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Apidra

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially ‘sodium-free’.

Apidra contains metacresol, which may cause allergic reactions.

3. HOW TO USE APIDRA

Dose

Based on your life-style and the results of your blood sugar (glucose) tests and your previous insulin usage, your doctor will determine how much Apidra you will need.

Always use Apidra exactly as your doctor has told you. You should check with your doctor if you are not sure.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate, long acting insulin, a basal insulin or with tablets used to treat high blood sugar levels.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Method of administration

Apidra is injected under the skin (subcutaneously).

Your doctor will show you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. The effect will be slightly quicker if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

Frequency of administration

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Instructions for proper use

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing insulin glulisine.

Read carefully the "SoloStar Instructions for use" included in this package leaflet. You must use the pen as described in these Instructions for use.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Before use always attach a new needle, and perform a safety test. Only use needles that are compatible for use with SoloStar (see “SoloStar Instructions for use”).

Look at the cartridge sealed in the disposable pen injector before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Do not shake or mix it before use.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with SoloStar, please consult your Health Care Professional.

If you use more Apidra than you should

- If you **have injected too much Apidra**, your blood sugar level may become too low (hypoglycaemia).
Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Apidra

- If you **have missed a dose of Apidra** or if you **have not injected enough insulin,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.

- Do not take a double dose to make up for a forgotten dose.

If you stop using Apidra

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Apidra without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can cause side effects, although not everybody gets them.

Hypoglycaemia (low blood sugar) can be very serious. If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar, take actions to increase your blood sugar level **immediately.**

<u>If you experience the following symptoms, contact your doctor immediately:</u>
large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. These could be symptoms of **generalised allergy to insulin, including anaphylactic reaction, which may be life-threatening.**

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Very common reported side effects
- Hypoglycaemia

Hypoglycaemia (low blood sugars) means that there is not enough sugar in the blood.
See the box at the end of this leaflet for important further information about hypoglycaemia and its treatment.

Common reported side effects

- Skin and allergic reactions

Reactions at the injection site may occur (such as reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Uncommon reported side effects

- Systemic allergic reactions

Generalised allergy to insulin. Associated symptoms may include large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

Rare reported side effect

- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.

Other side effects (frequency not known) include:

- **Hyperglycaemia (high blood sugars) means there is too much sugar in the blood**

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. See the box at the end of this leaflet for further information.

- **Eye reactions**

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE APIDRA

Keep out of the reach and sight of children.
Do not use Apidra after the expiry date, which is stated on the carton and on the label of the pen. The expiry date refers to the last day of that month.

Not in-use pens
Store in a refrigerator (2°C-8°C). Do not freeze. Do not put SoloStar next to the freezer compartment or a freezer pack.

Keep the pre-filled pen in the outer carton in order to protect from light.

In-use pens
Pre-filled pens in use (or carried as a spare) may be stored for a maximum of 4 weeks below 25°C and away from direct heat or direct light. The pen in use must not be stored in a refrigerator.

Do not use it after this time period.

Do not use Apidra if it does not appear clear and colourless.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Apidra contains

- The active substance is insulin glulisine. Each ml of the solution contains 100 Units of insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

What Apidra looks like and contents of the pack

Apidra 100 Units/ml, solution for injection in a pre-filled pen, SoloStar. It is a clear, colourless, aqueous solution with no particles visible.

Each pen contains 3 ml solution, equivalent to 300 Units. Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pre-filled pens are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder**:**
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Manufacturer:
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This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency (EMEA) web site: http://www.emea.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are a person with diabetes.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?
Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Using other medicines").

Warning symptoms of hyperglycaemia
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia?
Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occurs?
Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Using other medicines").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast : sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

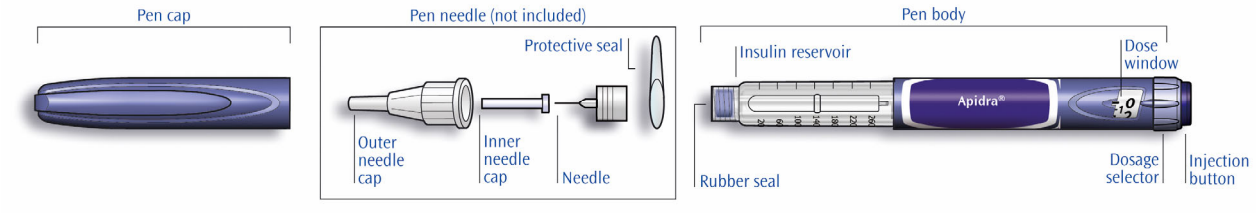
Apidra solution for injection in a pre-filled pen. SoloStar. INSTRUCTIONS FOR USE

SoloStar is a prefilled pen for the injection of insulin. Your healthcare professional has decided that SoloStar is right for you. Talk with your healthcare professional about proper injection technique before using SoloStar.

Read these instructions carefully before using your SoloStar. If you are not able to follow all the instructions completely on your own, use SoloStar only if you have help from a person who is able to follow the instructions. Hold the pen as shown in this leaflet. To ensure that you read the dose correctly, hold the pen horizontally, with the needle on the left and the dosage selector to the right as shown in the illustrations below.

You can set doses from 1 to 80 units in steps of 1 unit. Each pen contains multiple doses.

Keep this leaflet for future reference.
If you have any questions about SoloStar or about diabetes, ask your healthcare professional or call the local sanofi-aventis number on the front of this leaflet.



Schematic diagram of the pen

Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that are compatible for use with SoloStar.
- Always perform the safety test before each injection (see Step 3).
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. The Apidra SoloStar is blue. It has a dark blue injection button with a raised ring on the top.

B. Take off the pen cap.

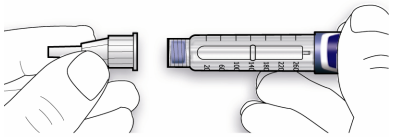
C. Check the appearance of your insulin. Apidra is a clear insulin. Do not use this SoloStar if the insulin is cloudy, coloured or has particles.

Step 2. Attach the needle

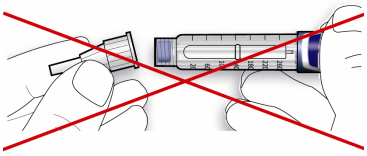
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



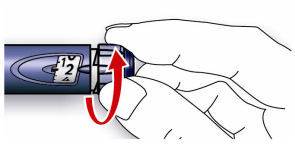
- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or damage the needle.



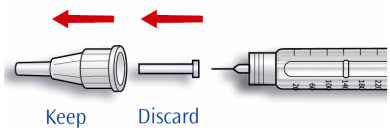
Step 3. Perform a Safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:
- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.



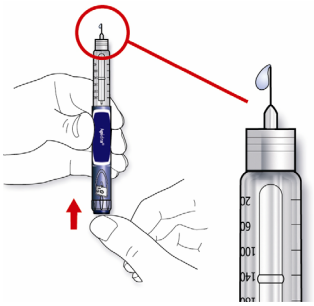
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

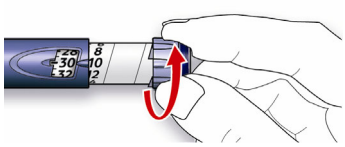
- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.



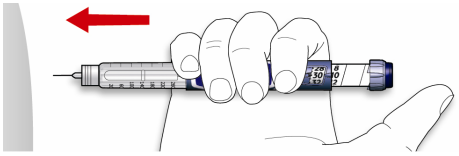
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

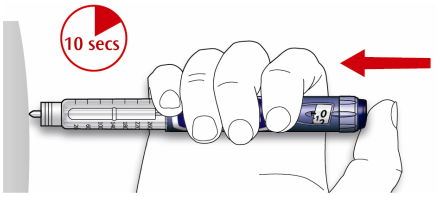
Step 5. Inject the dose

A. Use the injection method as instructed by your healthcare professional.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.



D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

The pen plunger moves with each dose. The plunger will reach the end of the cartridge when the total of 300 units of insulin have been used.

Step 6. **Remove** and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:

- Contamination and/or infection,
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

B. Dispose of the needle safely, as instructed by your healthcare professional.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.